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(54) DERIVATIVES OF PHYSIOLOGICALLY ACTIVE SUBSTANCE K-252.

(57) Novel derivatives of K-252 {(8R*, 9S*, 11S*)-(-)-9-hydroxy-9-methoxycarbonyl-8-methyl-2,3,9,10-tetrahydro-8,11-epoxy-1H,8H,11H-2,7b,11a-triazadibenzo[a,g]cycloocta[cde]trinden-1-one} represented by formula (I) (wherein W_1, W_2, R^1, R^2, R^3, R^4, X, and Y represent various substituents) are disclosed. These compounds are physiologically active substances having a protein kinase C-inhibiting activity and an oncostatic activity, thus being useful as medicines.

EP 0 303 697 A1

Isolation and purification of the product after completion of each step described above can be carried out by methods used in conventional organic synthesis, for example, by an appropriate combination of extraction, crystallization, chromatography, etc.

Compound (I) shows a marked cell growth inhibitory activity against human uterine cervical cancer HeLa cells, human breast cancer cell MCF 7, human colon adenocavcinoma cell COLO320DM and human lung differented squamous cell carcinoma cell PC-10, and accordingly, anti-tumor compositions comprising Compound (I) as an effective ingredient are provided.

Compound (I) and its pharmacologically acceptable salts include oleophilic and hydrophilic ones and such properties are particularly preferred for pharmaceutical use in some cases. In cases where Compound (I) is used as an anti-tumor composition, each compound is dissolved in physiological saline or a solution of glucose, lactose or mannitol for injection, and usually intravenously administered as an injection in a dose of 0.01 to 20 mg/kg. Alternatively, the compound may be freeze-dried in accordance with the Japanese Pharmacopoeia or may be prepared into injectable powder by adding sodium chloride thereto. Further, the anti-tumor composition may also contain pharmacologically acceptable well-known diluents, adjuvants and/or carriers such as salts which satisfy requirements for medical use. In cases where the compound is used as an injection, it is sometimes preferred to use auxiliary agents which enhance the solubility. Doses may be appropriately varied depending upon the age and conditions. Administration schedule can also be varied depending upon the conditions and dose. For example, the compound is administered once a day (by single administration or consecutive administration) or intermittently one to three times a week or once every three weeks. Further, oral administration and rectal administration are also possible in the same dose and in the same manner.

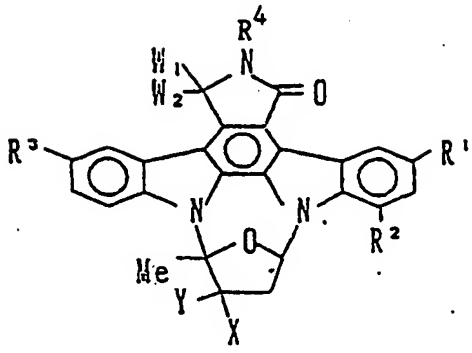
The compound can be administered, with appropriate adjuvants, as tablets, powders, granules, syrup, etc. for oral administration and as suppositories for rectal administration.

Examples

Representative examples of Compound (I) obtained by the processes described above are shown in Table 2 and the intermediates thereof are shown in Table 3.

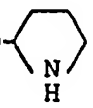
Examples of preparation of the Compound (I) and the intermediates are respectively shown in Examples and Reference Examples. Compound Nos. correspond to Example Nos.

Table 2



[I]

Compound No.	R^1	R^2	R^3	R^4	W_1 W_2	X	Y
1	H	H	H	H	H	CONHOH	OH
2	H	H	H	H	H	$CONH_2$	OH
3	H	H	H	H	H	$CONHCH_2CH_2OH$	OH
4	H	H	H	H	H	CO_2Et	OH
5	H	H	H	Cl	H	CO_2Me	OH
6	Cl	H	H	H	H	CO_2Me	OH
7	Br	H	H	H	H	CO_2Me	OH
8	H	H	H	$CONH_2$	H	CO_2Me	OH
9	NH_2	H	H	H	H	CO_2Me	OH
10	NH_2	H	NH_2	H	H	CO_2Me	OH
11	H	NH_2	H	H	H	CO_2Me	OH
12	NMe_2	H	H	H	H	CO_2Me	OH
13	NHCONHMe	H	H	H	H	CO_2Me	OH
14	$NHCONH_2$	H	H	H	H	CO_2Me	OH
15	OH	H	H	H	H	CO_2Me	OH
16	OH	H	OH	H	H	CO_2Me	OH

Compound No.	R^1	R^2	R^3	R^4	W_1 W_2	X	Y
17	On-Pr	H	H	H	H	CO_2Me	OH
18	CH_2OH	H	H	H	H	CO_2Me	OH
19	Me	H	H	H	H	CO_2Me	OH
20	H	H	H	H	H	CH_2OH	OH
21	OH	H	H	H	H	CH_2OH	OH
22	Cl	H	H	H	H	CH_2OH	OH
23	NH_2	H	H	H	H	CH_2OH	OH
24	Br	H	H	H	H	CH_2OH	OH
25	OH	H	OH	H	H	CH_2OH	OH
26	Me	H	H	H	H	CH_2OH	OH
27	H	H	H	H	H	$CH_2OCOCH_2CH_2CO_2H$	OH
28 *)	H	H	H	H	H	CH_2O- 	OH
29	H	H	H	H	H	CH_2N_3	OH
30	H	H	H	H	H	CH_2NH_2	OH
31	H	H	H	H	H	$CH_2NHCH_2CO_2Me$	OH
32	H	H	H	H	H	$CH_2NHCH_2CO_2H$	OH
33	H	H	H	H	H	$CH_2N=CH-NMe_2$	OH
34	H	H	H	H	H	$CH_2NHCOCH_2NH_2$	OH
35	H	H	H	H	H	CH_2NHCO- 	OH
36	H	H	H	H	H		$-CH_2O-$
37	H	H	H	H	H	CH_2NHMe	OH
38	H	H	H	H	H	CH_2N 	OH